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BARRETT'S ESOPHAGUS AND THE RISK OF ADENOCARCINOMA

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BARRETT'S ESOPHAGUS AND THE RISK OF ADENOCARCINOMA THESIS FOR DOCTORAL DEGREE (PhD)

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ABSTRACT

Barrett's esophagus is the precursor lesion of esophageal adenocarcinoma, a tumor with increasing incidence and poor prognosis. The overall aim of the thesis was to assess risk and prognosis in patients with Barrett's esophagus and esophageal adenocarcinoma. Four studies were conducted based on data from Swedish nationwide registers and medical records from 71 Swedish hospitals.

Study I was a population-based cohort study which assessed the risk of esophageal adenocarcinoma among patients with Barrett's esophagus. Among 7,932 study participants with Barrett's esophagus (median age 66 years, 68% men), 89 developed esophageal adenocarcinoma. After excluding prevalent adenocarcinomas (70%), 27 adenocarcinomas developed over a period of 18,415 person-years, which corresponded to an incidence rate of 1.5 (95% CI 0.9-2.0) cases per 1,000 person-years at risk and a standardized incidence ratio of 9.4 (95% CI 6.2-13.6).

Study II was a population-based, nested case-control study designed to identify a prediction model for progression from Barrett's esophagus to adenocarcinoma or high-grade dysplasia. All adenocarcinoma and high-grade dysplasia in patients with Barrett's esophagus in Sweden were included as cases (n=279). Four randomly selected non-progressors per case were included as controls (n=1,089). For the included patients, endoscopy and histopathology records were collected and reviewed. Older age, male sex and longer Barrett's esophagus segment length were associated with increased risk of adenocarcinoma/high-grade dysplasia. In contrast, hiatal hernia and esophagitis were not associated with tumor progression. A model based on age, sex and segment length predicted 71% of adenocarcinoma/high-grade dysplasia.

Study III was a population-based cohort study which evaluated the adherence to surveillance and treatment guidelines for Barrett's esophagus. All patients with dysplastic Barrett's esophagus in Study II were included and followed for median 3.9 years using nationwide registers. Among 211 participants (71% low-grade dysplasia, 29% high-grade dysplasia), 84% had a follow-up endoscopy, 17% received endoscopic therapy and 8% underwent esophagectomy. However, 60% were not managed in accordance with clinical guidelines, mainly due to under-surveillance. Risk factors for deviation from surveillance and treatment recommended in guidelines were low-grade dysplasia compared to high-grade dysplasia and longer segment length compared to shorter segment length, while treatment in surgical

compared to gastroenterological departments was associated with recommended surveillance and treatment.

Study IV was a population-based cohort study which assessed whether endoscopy screening improves the prognosis of esophageal adenocarcinoma. Among 6,600 study participants with adenocarcinoma (mean age 70 years, 79% male) followed for 9,138 person-years, 7% had a history of gastroesophageal reflux disease and 9% underwent endoscopy before cancer diagnosis. The 5-year mortality was decreased in patients with history of gastroesophageal reflux disease (HR 0.71, 95% CI 0.64-0.80), and this decrease was only slightly attenuated by adjustment for prior endoscopy (HR 0.79, 95% CI 0.70-0.90). The 5-year mortality was unchanged in patients with 1-2 screening endoscopies (compared to patients without screening endoscopy), while those with ≥ 3 endoscopies for gastroesophageal reflux disease had improved survival in esophageal adenocarcinoma (HR 0.55, 95% CI 0.36-0.85).

To conclude, the overall risk of adenocarcinoma in Barrett's esophagus is low, but it is possible to predict a clearly higher risk of tumor progression based on a few clinically available risk factors, enabling tailored endoscopy surveillance in these patients. Currently, adherence to recommended surveillance and treatment guidelines is poor, and efforts to implement these guidelines in clinical practice are needed. Use of endoscopy screening has a limited impact on survival in adenocarcinoma unless performed frequently.

LIST OF SCIENTIFIC PAPERS

- I. Holmberg D, Ness-Jensen E, Mattsson F, El-Serag HB, Lagergren J.
Risk of oesophageal adenocarcinoma in individuals with Barrett's oesophagus.
European Journal of Cancer 2017;75:41-45
- II. Holmberg D, Ness-Jensen E, Mattsson F, Lagergren J.
Clinical prediction model for tumor progression in Barrett's esophagus.
Surgical Endoscopy 2018 (in press)
- III. Holmberg D, Ness-Jensen E, Mattsson F, Lagergren J.
Adherence to clinical guidelines for Barrett's esophagus.
Manuscript submitted
- IV. Holmberg D, Ness-Jensen E, Mattsson F, Lagergren J.
Endoscopy for gastroesophageal reflux disease and survival in esophageal adenocarcinoma.
Manuscript submitted

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1 INTRODUCTION

Barrett's esophagus, a conversion from normal esophageal squamous epithelium to metaplastic columnar epithelium, develops due to chronic gastroesophageal reflux disease (GERD) and is prevalent in 1-2% of the population. Barrett's esophagus is relevant as the precursor lesion of esophageal adenocarcinoma, a tumor with increasing incidence and poor prognosis. Because of the malignant potential, patients diagnosed with Barrett's esophagus are enrolled in endoscopic surveillance to detect high-grade dysplasia or early adenocarcinoma. However, only a minute proportion of patients with Barrett's esophagus will develop adenocarcinoma, and there is a great need to identify those at particularly high or low risk to better tailor the follow-up of these patients.

This thesis contains four original studies of patients with Barrett's esophagus and esophageal adenocarcinoma. These studies are based on nationwide medical registers linked to data from collected endoscopy and histopathology reports. The first study addresses the absolute risk of adenocarcinoma in Barrett's esophagus. The second study provides a prediction model for tumor progression among patients with Barrett's esophagus. The third study evaluates the adherence to surveillance and treatment guidelines for Barrett's esophagus in clinical practice and the fourth study assesses whether use of endoscopy screening improves survival in esophageal adenocarcinoma.

2 BACKGROUND

2.1 STRUCTURE AND FUNCTION OF THE ESOPHAGUS

The esophagus is an approximately 25 cm long and 2 cm wide muscular tube which connects the pharynx to the stomach. Its course is relatively straight, beginning posterior to the trachea and continuing down in front and slightly to the left of the vertebral column. The esophagus then passes through the posterior mediastinum behind the heart before exiting the thorax through the diaphragm.¹ Its upper and lower ends are supplied with two sphincters which open during swallowing or vomiting. In addition, the lower esophageal sphincter functions as a reflux barrier, protecting the esophagus from acidic reflux from the stomach. From its lumen and out, the esophagus is divided into four tissue layers: mucosa, submucosa, muscularis propria and adventitia (but no serosal layer).² The lumen is normally lined by stratified squamous epithelium, which is supported by the lamina propria and the connective tissue of the submucosa. Through an endoscope, the transition to stomach is demarcated by the gastric folds, which signals the border where the esophagus ends and the stomach begins. The transition from squamous to gastric columnar epithelium, and thus from esophagus to stomach, is visually apparent as a change in color from white to pink.

2.2 THE AXIS OF PATHOLOGY: GASTROESOPHAGEAL REFLUX DISEASE, BARRETT'S ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

2.2.1 Gastroesophageal reflux disease

GERD is defined as “a condition that develops when the reflux of stomach contents causes troublesome symptoms and complications” according to a consensus definition (the Montreal definition).³ GERD is one of the most common health disorders with a prevalence of 15-25% of adults in Western countries.^{4,5} The diagnosis can often be established based on a medical history with typical symptoms, i.e. heartburn or regurgitation, in combination with a positive response to anti-reflux medication with proton pump inhibitors.⁶ Severe GERD resistant to medication may be treated with surgery, i.e. fundoplication.^{7,8}

Although GERD is generally considered a benign condition associated with mildly impaired quality of life, it may also cause potentially life-threatening complications.^{9,10} Chronic GERD is a potent risk factor for esophageal adenocarcinoma, a tumor arising in the distal esophagus with very poor prognosis.^{11,12} Esophageal adenocarcinoma is preceded by Barrett's

esophagus, which is a metaplasia from the normal esophageal squamous epithelium to columnar epithelium. Barrett's esophagus is typically visible upon standard white light endoscopy as a pink area stretching above the gastroesophageal junction.¹³

2.2.2 Barrett's esophagus

2.2.2.1 History

The condition is named after the Australian thoracic surgeon Norman Barrett, who described a columnar-lined esophagus in the case report "*Chronic peptic ulcer of the oesophagus and 'oesophagitis'*," published in 1950.¹⁴ In the report, Barrett described the esophageal specimen of a young boy with an esophageal ulcer and surrounding columnar epithelium extending to the level of the aortic arch (Figure 1). This was likely not the first description of a columnar-lined esophagus, as Barrett cited several previous case reports in his original study. Some contend that the first description was made in 1906 by the American pathologist Wilder Tileston, who described three cases of esophageal peptic ulcer and noted "the close resemblance of the mucous membrane about the ulcer to that normally found in the stomach," also correctly attributing the cause of the lesion to gastroesophageal reflux.^{15, 16} Perhaps the most convincing early description of Barrett's esophagus was provided by Alexander Lyall in

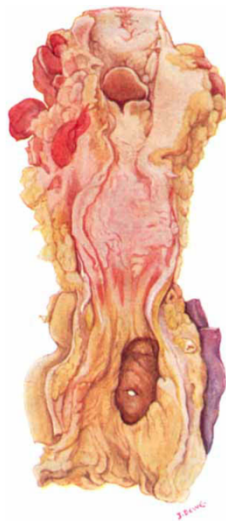


Figure 1. Illustration of the esophageal specimen described by Norman Barrett in 1950. The presence of gastric folds surrounding the ulcer suggests that the columnar epithelium originated from an intrathoracic stomach rather than the esophagus. Reproduced with permission from Barrett.¹⁴

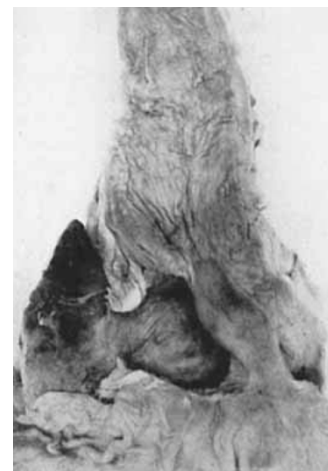


Figure 2. Photograph of the esophageal specimen described by Alexander Lyall in 1937. The dark zone extending above the ulcer represents one of the first descriptions of Barrett's esophagus. Reproduced with permission from Lyall.¹⁷

1937, who described the esophageal specimen of Patrick C, a 58-year old male with long-standing epigastric pain, weight loss, anemia and occasional vomiting of coffee ground material (Figure 2).¹⁷ Patrick C died from a bleeding esophageal ulcer, but Lyall noted that the mucosa surrounding the ulcer was “heterotopic gastric mucosa which extended as a tongue-shaped process of well-preserved tissue upwards from that of the fundus of the stomach,” a typical description of Barrett’s esophagus.¹⁷ Although Barrett did not claim to be the first to describe esophageal columnar epithelium or ulcers in such epithelium, Allison and Johnstone named the ulcers “Barrett’s ulcer” in a subsequent article in *Thorax*.¹⁸ By extension, the surrounding epithelium became known as Barrett’s esophagus.^{16, 19}

2.2.2.2 Definition and risk factors

Barrett’s esophagus develops as a consequence of chronic gastroesophageal reflux to the lower esophagus, which induces an inflammatory response and a replacement of damaged esophageal squamous epithelium with acid-resistant columnar epithelium.¹³ A suspected diagnosis of Barrett’s esophagus is verified by biopsy, which may show three distinct forms of columnar epithelium: intestinal-type, cardia-type and gastric fundic-type. Most medical societies require intestinal-type epithelium, which contains prominent goblet cells, for the diagnosis of Barrett’s esophagus.²⁰⁻²³ This requirement is debated, and UK guidelines (among others) consider all metaplastic columnar epithelium above the gastroesophageal junction as Barrett’s esophagus.²⁴ Compared to intestinal-type epithelium, cardia-type and gastric fundic-type epithelium entail a lower risk of adenocarcinoma development.²⁵ Until the late 1990s, Barrett’s esophagus was only considered for columnar epithelium extending an arbitrary 3 cm or more proximally, nowadays termed long-segment Barrett’s esophagus in contrast to short-segment Barrett’s esophagus (shorter than 3 cm). Today, the metaplastic area is often described in a standardized manner according to the Prague C & M criteria, which outline the circumferential and maximum extent of the segment.²⁶

The metaplastic epithelium is further classified by the reviewing pathologist for presence and degree of dysplasia. The vast majority of Barrett’s esophagus is negative for dysplasia, which is associated with the lowest risk of esophageal adenocarcinoma.^{27, 28} Dysplastic lesions are categorized into low-grade or high-grade dysplasia, which are more immediate precursor lesions of adenocarcinoma and entail a higher risk of tumor progression. The annual risk of adenocarcinoma in low- and high-grade dysplasia is approximately 0.6% and 7%, respectively, although the reported risk of tumor progression differs substantially between studies.^{29, 30} The heterogeneity between studies is likely in part due to difficulties of

accurately determining degree of dysplasia.^{31, 32} A small proportion of biopsy specimens are classified as indefinite for dysplasia, which is a poorly studied condition. The risk of adenocarcinoma in these lesions seems to be somewhere between the risk in Barrett's esophagus negative for dysplasia and low-grade dysplasia.³³

Barrett's esophagus is prevalent in 1-2% of Western and Asian populations,³⁴⁻³⁶ but more frequently in those with GERD, in men, and in the elderly.³⁷⁻³⁹ Long segments are closely related to GERD symptoms, while short-segment disease often is asymptomatic.⁴⁰ Short-segment Barrett's esophagus is more prevalent in the population, but often remains undiagnosed.^{34, 35} Obesity, in particular a central distribution of adipose tissue, increases the risk of Barrett's esophagus by promoting GERD through mechanical effects on the lower esophageal sphincter, but may also increase the risk through the release of cytokines and growth factors from adipose tissue.^{41, 42} Weight loss decreases GERD, but whether the risk of Barrett's esophagus decreases reciprocally is uncertain.⁴³ Cigarette smoking increases the risk of Barrett's esophagus in a dose-dependent manner, in part by relaxing the lower esophageal sphincter and increasing GERD.⁴⁴ Infection with the bug *Helicobacter pylori* may lead to atrophy of the gastric corpus, thus decreasing production of gastric acid and the risk of Barrett's esophagus.^{45, 46} Barrett's esophagus also has a polygenic hereditary component and familial forms may be present in a minority of cases.⁴⁷

2.2.2.3 *Surveillance and treatment*

Most patients with Barrett's esophagus are followed with regularly spaced surveillance endoscopy with the purpose of detecting development of dysplasia or cancer at a curable stage and available for less extensive treatment. Based on the low absolute risk of progression, Barrett's esophagus negative for dysplasia is followed every 3-5 years while those with dysplasia are followed more often or endoscopically treated outright.²⁰⁻²⁴ Patients enrolled in surveillance programs are diagnosed with adenocarcinoma at younger age and earlier tumor stage, which translates into improved survival.⁴⁸⁻⁵² However, some of the improved survival associated with surveillance of Barrett's esophagus may likely be attributed to lead and length time bias.^{52, 53} Large population-based studies in recent years have indicated that the risk of tumor progression to adenocarcinoma in Barrett's is lower than previously reported, why the effectiveness and necessity of general surveillance have been questioned.^{54, 55}

Patients with Barrett's esophagus are typically administered anti-reflux medication with proton pump inhibitors regardless of reflux symptoms. Proton pump inhibitors block the

H⁺/K⁺ ATPase enzyme of the gastric parietal cells, which normally transports hydrogen ions to the gastric lumen where it forms hydrochloric acid. The immediate effect is a decreased acidity of the gastric contents, which limits tissue injury to the esophageal epithelium. Proton pump inhibitors are generally considered safe^{56, 57} and most observational studies have indicated that use of these medications also decrease the risk of progression from Barrett's esophagus to adenocarcinoma.⁵⁸⁻⁶¹ However, a recent randomized trial failed to show a dose-response effect of the proton pump inhibitor esomeprazole in preventing adenocarcinoma, which would be expected from a chemopreventive medication.⁶²

In addition, large-scale observational studies have indicated that use of aspirin and statins, which have anti-inflammatory properties, may prevent development of several forms of cancer, including esophageal adenocarcinoma.⁶³⁻⁶⁸ However, these preventive effects have not been reproduced convincingly in more recent studies.^{62, 69}

In the recent decade, the treatment arsenal available to physicians managing dysplastic Barrett's esophagus has expanded. Patients with low-grade dysplasia previously underwent frequent surveillance endoscopy, but are now considered for endoscopic eradication therapy with radiofrequency ablation, which seems more effective than surveillance for the prevention of adenocarcinoma.⁷⁰⁻⁷² High-grade dysplasia, previously treated with esophagectomy, is now treated with endoscopic methods, not the least radiofrequency ablation, which has superior efficacy to surveillance and is less invasive than open surgery.^{73, 74} Mucosal irregularities in a dysplastic segment are generally treated with endoscopic mucosal resection or endoscopic submucosal dissection, which also aids staging of the tumor by determining invasion depth.⁷⁵

2.2.3 Esophageal adenocarcinoma

Esophageal adenocarcinoma arises from Barrett's esophagus (columnar cells in the distal esophagus) and is thus often located in close proximity to the gastroesophageal junction. Once a true clinical rarity, the incidence of adenocarcinoma has increased manifold since the 1970s and had by the 1990s surpassed squamous cell carcinoma as the most common subtype of esophageal cancer in many Western countries.⁷⁶⁻⁷⁸ In 2012, 52,000 new cases of esophageal adenocarcinoma occurred worldwide, translating to an age-standardized incidence rate of 0.7 per 100,000 person-years at risk, but the tumor is considerably more common in developed countries (Figure 3).^{78, 79} Peak incidence occurs in Northern Europe, where almost 50% of all cases are diagnosed.⁷⁹

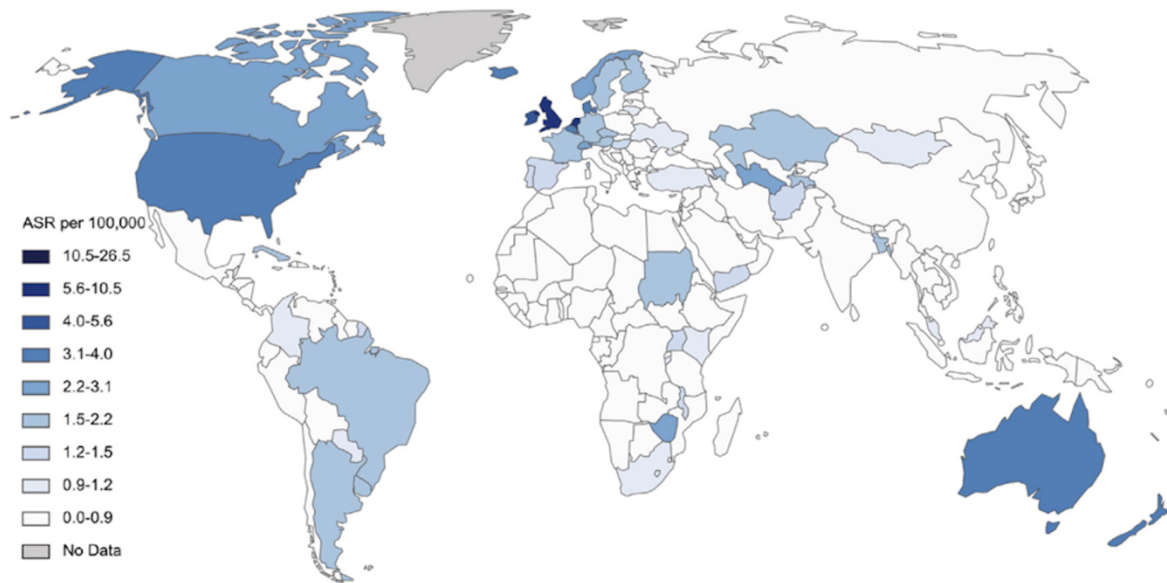


Figure 3. Global differences in age-standardized incidence rate (ASR) per 100,000 in men. Reproduced with permission from Arnold et al.⁷⁹

Risk factors for adenocarcinoma vastly overlap with those of Barrett's esophagus, including old age, male sex, GERD, obesity, and tobacco smoking, while infection with *Helicobacter pylori* seems to be protective for adenocarcinoma development.^{12, 42, 80, 81} GERD, which is the strongest risk factor, increases the risk by five to eight times, but is not reported by 40% of patients with adenocarcinoma.^{11, 12} The tumor has a pronounced male predominance, although the sex ratio varies considerably across geographical regions.⁷⁹ The excess risk for men in the US is 9:1, which is stronger than in any other non-sex-specific cancer.⁸² The cause of the male predominance remains largely unclear, but the increased severity of GERD and the higher prevalence of abdominal obesity and tobacco use among men might contribute. Sex hormonal factors may also explain some of the strong male predominance.⁸³

Upper endoscopy with biopsy is the gold standard for confirming the diagnosis of adenocarcinoma. Although GERD is the most frequent indication for referral to endoscopy, the increased use of endoscopy screening has had a modest or non-existent effect on tumor stage in patients diagnosed with adenocarcinoma (Figure 4).^{84, 85} Early symptoms of adenocarcinoma are scarce and >75% of patients present with advanced disease, when symptoms such as dysphagia, weight loss and fatigue become apparent.⁸⁵ Nevertheless, the overall 5-year survival in esophageal adenocarcinoma has increased from 5% in the 1960s to 20% today in Europe and the US, in part due to improvements in curatively intended treatment.^{86, 87}

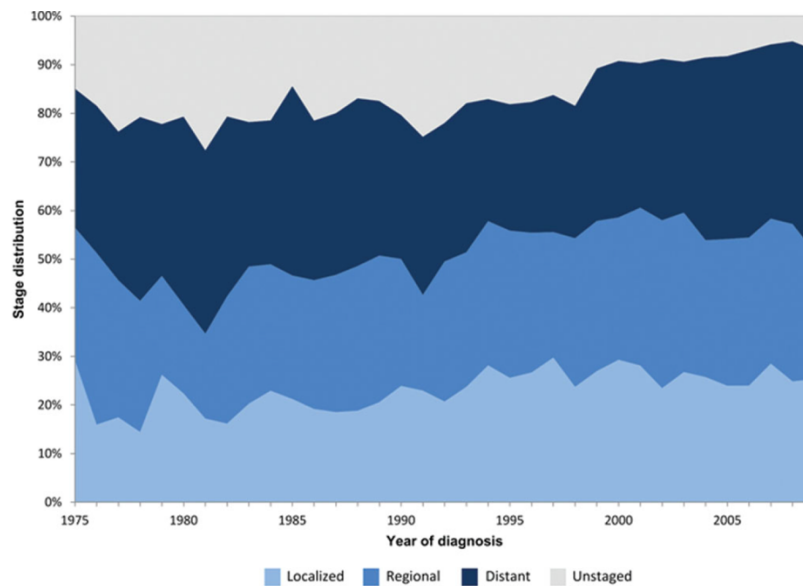


Figure 4. Stage distribution of incident cases of esophageal adenocarcinoma between 1975 and 2009 based on SEER data from the US. Reproduced with permission from Hur et al.⁸⁵

Tumor stage is assessed by endoscopy, endoscopic ultrasound, computed tomography and positron emission tomography. Endoscopic resection may provide a sample collection for T-staging and histopathological assessment in early tumors.⁸⁸ Superficial lesions confined to the mucosa (T1a) permits endoscopic resection followed by eradication of the remaining Barrett's esophagus segment, which decreases the risk of recurrence.⁸⁹ Tumors invading deep into the submucosa or further into the muscularis propria are treated with esophagectomy.^{76, 77} In locally advanced tumors (T3), surgery is generally preceded by neoadjuvant chemo- or chemoradiotherapy, which improves survival compared to surgery alone.^{90, 91} Esophagectomy is usually performed by a combined laparotomy or laparoscopy and thoracotomy or thoracoscopy and sometimes also a neck incision, where most of the esophagus is resected and replaced by a gastric conduit (or a colon interposition) anastomosed to the remaining proximal esophagus.⁷⁷ For tumors invading the tissue surrounding the esophagus (T4), distant metastatic disease or in patients not fit to undergo surgery, palliative treatment with chemo- or chemoradiotherapy is the treatment of choice, while stenting may be used to relieve dysphagia.^{76, 77}

3 AIMS

The overall aim of the thesis was to assess risk and prognosis among patients with Barrett's esophagus and esophageal adenocarcinoma.

The specific aims of the included studies were:

- To assess the absolute risk of esophageal adenocarcinoma in patients with Barrett's esophagus.
- To develop a model which predicts esophageal adenocarcinoma and high-grade dysplasia in patients with Barrett's esophagus.
- To evaluate adherence to surveillance and treatment guidelines for Barrett's esophagus in clinical practice.
- To assess whether use of endoscopy screening of GERD facilitates early detection of esophageal adenocarcinoma and thus improves survival in this cancer.

4 METHODS

4.1 OVERVIEW

Table 1. Methods overview of the included studies.

	Study I	Study II	Study III	Study IV
Short title	Risk of adenocarcinoma in Barrett's	Prediction model for adenocarcinoma in Barrett's	Adherence to guidelines in Barrett's	Endoscopy use and survival in adenocarcinoma
Design	Population-based cohort study	Population-based nested case-control study	Population-based cohort study	Population-based cohort study
Data sources	Patient Register, Cancer Register, Register of the Total Population	Patient Register, Cancer Register, Prescribed Drug Register, medical records	Patient Register, Cancer Register, Cause of Death Register, Prescribed Drug Register, medical records	Patient Register, Cancer Register, Cause of Death Register
Study participants	Barrett's esophagus	Barrett's esophagus	Barrett's esophagus	Esophageal adenocarcinoma
Exposure	Barrett's esophagus	Age, sex, segment length, hiatal hernia, esophagitis	Age, sex, comorbidity, degree of dysplasia, segment length, calendar period, department, hospital	GERD, endoscopy
Main outcome	Esophageal adenocarcinoma	Esophageal adenocarcinoma/ high-grade dysplasia	Deviation from surveillance guidelines	Disease-specific 5-year mortality
Secondary outcome(s)	Esophageal adenocarcinoma/ high-grade dysplasia	Esophageal adenocarcinoma, high-grade dysplasia	Under-surveillance, over-surveillance	All-cause 5-year mortality, surgical resection
Inclusion period	2006-2013	2006-2013	2006-2013	1997-2013
End of follow-up	2014	2014	2014	2016
Main statistical analysis	Standardized incidence ratio	Multivariable logistic regression, prediction modelling	Multivariable logistic regression	Multivariable Cox regression, logistic regression

Abbreviations: GERD – gastroesophageal reflux disease

4.2 DATA SOURCES

The studies in this thesis were based on data from two main sources: nationwide Swedish registers and medical records collected from hospitals managing patients with Barrett's esophagus. The registers and medical records were linked by the personal identity number, which was used for patient identification in both data sources as well as for data linkages. A personal identity number is assigned to all people permanently residing in Sweden and is unique to each individual.

4.2.1 The Patient Register

The Patient Register was established in 1964-1965 and was nationwide from 1987. The register is held by the National Board of Health and Welfare and contains demographic data, such as patient age and sex, diagnoses according to the International Classification of Diseases (ICD), procedures and information on the treating healthcare from all specialized out-hospital healthcare (from 2001) and in-hospital healthcare. Diagnoses and procedures are coded and registered by the discharging physician and electronically transferred to the National Board of Health and Welfare. Data from the Patient Register have been validated for their usefulness in population-based studies and diagnostic codes linked to procedures are generally well covered.⁹²

4.2.2 The Cancer Register

The Cancer Register was established in 1958 and contains data on all incident cancers in Sweden. The register holds tumor-specific data, such as site, histopathology, stage (since 2005) and date of diagnosis. The register has been validated for the registration of esophageal and gastric cardia adenocarcinoma with 98% completeness for registration, 100% completeness for histopathology reporting and 98% completeness for tumor stage.⁹³⁻⁹⁵

4.2.3 The Cause of Death Register

This register has recorded date and cause of all deaths in Swedish residents since 1952. The register is 100% complete for date of death and 99% complete for cause of death.^{96, 97} Cause

of death is registered on a yearly basis with a time lag, while date of death is continuously updated.

4.2.4 The Prescribed Drug Register

This register was started in July 2005 and holds data about all prescribed drugs in Sweden. The register is electronically recorded by Swedish pharmacies and quality controlled by the Swedish eHealth Agency. Given the automaticity and quality control, the accuracy and completeness of the register data are almost 100%.⁹⁸

4.2.5 The Register of the Total Population

This register holds information about date of birth, date of death, date of emigration and current residency status, and is continuously updated. This register was used for censoring purposes.

4.2.6 Medical records

Endoscopy and histopathology reports of 1,368 patients with Barrett's esophagus were obtained from 71 Swedish hospitals and manually reviewed. Data on date and indication for endoscopy, length of the Barrett's esophagus segment, hiatal hernia and esophagitis were extracted from the endoscopy reports. The histopathology reports were assessed for metaplasia, dysplasia and inflammation.

4.3 STUDY DESIGN

4.3.1 Study I

4.3.1.1 Design

This was a population-based cohort study of all patients with a recorded diagnosis of Barrett's esophagus in the Swedish Patient Register during the study period. Data were

retrieved from the Patient Register, the Cancer Register and the Register of the Total Population.

4.3.1.2 Study cohort

The study cohort was identified by the ICD code for Barrett's esophagus in the Patient Register between January 1, 2006 and December 31, 2013. Among 8,189 identified patients with Barrett's esophagus, those with missing information on date of diagnosis (n=4), younger than 30 years at diagnosis (n=99) or with a history of high-grade dysplasia or esophageal adenocarcinoma (n=154) were excluded from the study cohort, resulting in 7,932 patients available for analysis.

4.3.1.3 Outcome

The main outcome was esophageal adenocarcinoma, while the secondary outcome was the compound endpoint of adenocarcinoma or high-grade dysplasia. The outcomes were defined from the Cancer Register by the ICD codes for esophageal or gastric cardia cancer in combination with histology codes for adenocarcinoma or high-grade dysplasia.

4.3.1.4 Statistical analysis

Follow-up started on the date of Barrett's esophagus diagnosis and ended at adenocarcinoma or high-grade dysplasia diagnosis, death or end of study period, whichever occurred first. Incidence rates were calculated as cases per 1,000 person-years at risk with 95% confidence intervals (CI). For the main analysis, participants with adenocarcinoma or high-grade dysplasia within one year of Barrett's esophagus diagnosis were excluded, because these were considered to have prevalent cancer or dysplasia. Standardized incidence ratios (SIR) with 95% CI of adenocarcinoma were calculated to compare the risk in the Barrett's esophagus cohort with the expected risk assessed from the background population. The SIRs were calculated by dividing the observed number of adenocarcinomas in the Barrett's esophagus cohort by the expected number. The expected number was derived from the Cancer Register and defined as the number of adenocarcinoma cases that would occur in the Barrett's esophagus cohort if the incidence rate for adenocarcinoma was the same as of the background population of the same age, sex and calendar year. The expected number was obtained by multiplying the observed person-time by age (in 5-year groups), sex and calendar year-specific incidence rates in the general population.

4.3.2 Study II

4.3.2.1 Design

This was a population-based, nested case-control study in a cohort of patients with Barrett's esophagus. Data were retrieved from the Patient Register, the Cancer Register, the Prescribed Drug Register and from medical records.

4.3.2.2 Study cohort

Figure 5 shows a flowchart for the identification and selection of study participants. The study cohort was derived from the nationwide cohort of 8,189 patients diagnosed with Barrett's esophagus described in Study I. Cases were patients with esophageal adenocarcinoma or high-grade dysplasia as identified from the Cancer Register. Four controls per case were randomly identified from the remaining cohort without tumor progression during follow-up. The index date of Barrett's esophagus was identified, and endoscopy and histopathology reports from this date were retrieved from all hospitals managing these patients.

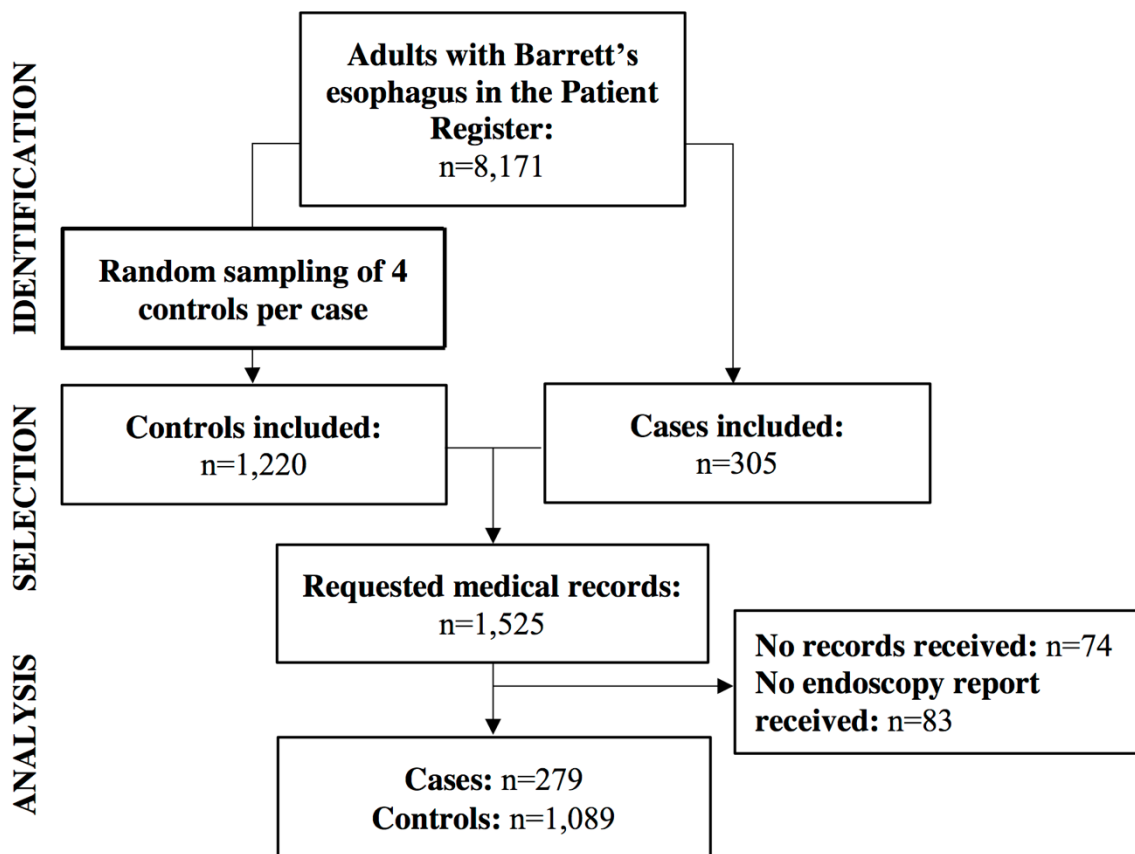


Figure 5. Flowchart of the selection of study participants available for final analysis in Study II.

4.3.2.3 Predictors of tumor progression

Five variables were considered to be potentially relevant for a prediction model: age, sex, length of the Barrett's esophagus segment, hiatal hernia and esophagitis. These variables were retrieved from the endoscopy report. In addition, the Patient Register was searched for previous diagnoses of hiatal hernia or reflux esophagitis.

4.3.2.4 Outcomes

The main outcome was the compound endpoint of adenocarcinoma or high-grade dysplasia, while secondary outcomes were adenocarcinoma or high-grade dysplasia separately. Adenocarcinoma and high-grade dysplasia were identified by the corresponding ICD and histology codes in the Cancer Register.

4.3.2.5 Statistical analysis

Logistic regression was used to determine crude and adjusted odds ratios (OR) with 95% CI for the association between all outcomes and the five potential predictors of tumor progression. For categorical variables, the assumed lowest risk category was used as reference. The accuracy of the model was assessed by fitting a receiver operating characteristic (ROC) curve. In addition to a complete case analysis, the main analysis used multiple imputation to address missing data on segment length (10%).

4.3.3 Study III

4.3.3.1 Design

This was a population-based cohort study of patients with dysplastic Barrett's esophagus. Data were retrieved from the Patient Register, the Cancer Register, the Cause of Death Register, the Prescribed Drug Register and from medical records.

4.3.3.2 Study cohort

Figure 6 shows a flowchart for the identification and selection of study participants. The study cohort consisted of all patients with dysplastic Barrett's esophagus identified in Study II. Excluded were patients with a history of esophageal adenocarcinoma, indefinite for dysplasia, dysplasia without evidence of specialized intestinal metaplasia and those ineligible

for surveillance because of a too short follow-up due to death, early diagnosis of adenocarcinoma or end of study period.

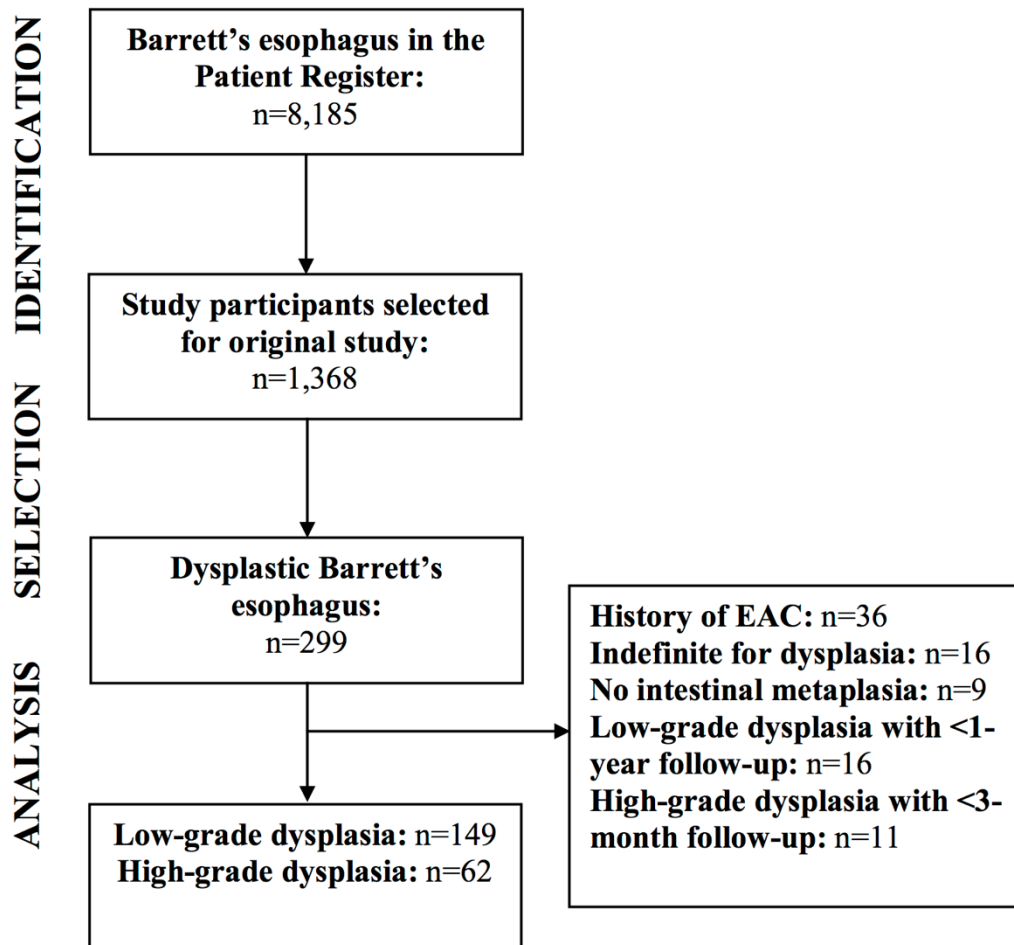


Figure 6. Flowchart of the selection of study participants available for final analysis in Study III. Abbreviations: EAC – esophageal adenocarcinoma.

4.3.3.3 Risk factors

Eight variables were considered as risk factors for deviation from guidelines: age, sex, comorbidity, degree of dysplasia, Barrett's esophagus segment length, calendar period, hospital type and department type. Comorbidities were accumulated and categorized according to the Charlson Comorbidity Index.⁹⁹

4.3.3.4 Outcomes

The main outcome was deviation from the surveillance and treatment recommended in clinical guidelines for dysplastic Barrett's esophagus.^{20, 22, 100-102} For patients with low-grade

dysplasia, adherence to guidelines was defined as repeat endoscopy with biopsy within 6-12 months of baseline assessment. Adherence to guidelines in patients with high-grade dysplasia was defined as repeated endoscopy with biopsy, endoscopic eradication therapy or esophagectomy within 3 months of baseline assessment. Management other than this was classified as deviation from guidelines. The secondary outcomes were under- and over-surveillance assessed separately. Under-surveillance was defined by either lack of endoscopic surveillance or treatment first after the recommended time interval. Over-surveillance was defined as repeat endoscopy before the recommended time interval. Data on endoscopy, endoscopic eradication therapy and esophagectomy were accessed from the Patient Register.

4.3.3.5 Statistical analysis

Follow-up started on the date of index endoscopy with biopsy and ended at date of death, diagnosis of esophageal adenocarcinoma or end of study period, whichever occurred first. Logistic regression was used to determine crude and adjusted ORs with 95% CI for the association between risk factors and outcomes. For categorical variables, the assumed lowest risk category was used as reference. The main model provided ORs adjusted for age, sex, segment length, comorbidity, calendar period, hospital and department.

4.3.4 Study IV

4.3.4.1 Design

This was a population-based cohort study of patients with esophageal adenocarcinoma in Sweden. Data were retrieved from the Patient Register, the Cancer Register and the Cause of Death Register.

4.3.4.2 Study cohort

The study cohort included all patients with a diagnosis of esophageal adenocarcinoma identified from the Cancer Register between January 1, 1997 and December 31, 2013. Participants with a diagnosis of Barrett's esophagus, who are enrolled in endoscopic surveillance, were excluded.

4.3.4.3 Exposures

GERD was identified in the Patient Register by a set of ICD codes, including heartburn, gastroesophageal reflux disease, esophagitis, esophageal ulcer and esophageal obstruction.

Endoscopy was identified in the Patient Register, where endoscopies within 10 years prior to adenocarcinoma were counted. GERD and endoscopy within 3 months of adenocarcinoma were censored in order to exclude early adenocarcinoma misclassified as GERD and to exclude any endoscopy part of the work-up of an already existing adenocarcinoma.

4.3.4.4 Confounders and mediators

Age, sex, calendar-year and comorbidity were adjusted for, where comorbidity was categorized using the Charlson Comorbidity Index.⁹⁹ Prior endoscopy, tumor stage and surgical resection were assessed as potential mediators between GERD and 5-year mortality.

4.3.4.5 Outcomes

The main outcome was disease-specific 5-year mortality, defined as the time from adenocarcinoma diagnosis until death specifically related to the tumor. Secondary outcomes were all-cause 5-year mortality and surgical resection of the tumor. All-cause 5-year mortality was defined as the time from adenocarcinoma diagnosis until death from any cause. Data on date and cause of death were retrieved from the Cause of Death Register. Surgical resection was defined by procedure codes corresponding to endoscopic or surgical resection of the esophagus or stomach in the Patient Register.

4.3.4.6 Statistical analysis

Follow-up started on the date of adenocarcinoma diagnosis and ended at date of death, end of study period or 5 years after cohort entry, whichever occurred first. The product limit estimates of the disease-specific 5-year survivor function were calculated for the exposures separately. Cox regression was used to determine crude and adjusted hazard ratios (HR) with 95% CI for the association between exposures and mortality outcomes. The odds of undergoing surgical resection were assessed using logistic regression, which provided crude and adjusted ORs with 95% CI. The main models provided HRs and ORs adjusted for age, sex, calendar year and comorbidity. To evaluate effect modification of GERD of the associations between endoscopy and the outcomes, an interaction term was included for GERD and endoscopy. The HR and OR were then calculated separately for patients with and without GERD.

5 RESULTS

5.1 STUDY I

Among 7,932 study participants with a diagnosis of Barrett's esophagus followed for 18,415 person-years, median age was 66 years and 68% were male (Table 2). During the follow-up, 89 study participants developed esophageal adenocarcinoma and 61 developed high-grade dysplasia. Most adenocarcinoma (n=62) and high-grade dysplasia (n=34) were diagnosed within one year of Barrett's esophagus diagnosis and were considered prevalent.

Table 2. Characteristics of 7,932 study participants with Barrett's esophagus.

	Number (%)
Age (years)	
30-49	866 (10.9)
50-69	4,209 (53.1)
≥70	2,857 (36.0)
Sex	
Women	2,572 (32.4)
Men	5,360 (67.6)
Adenocarcinoma	
≤1 year of Barrett's esophagus diagnosis	62 (69.7)
>1 year of Barrett's esophagus diagnosis	27 (30.3)
Median age at diagnosis (years)	70.0
High-grade dysplasia	
≤1 year of Barrett's esophagus diagnosis	34 (55.7)
>1 year of Barrett's esophagus diagnosis	27 (44.3)
Median age at diagnosis (years)	68.0

After excluding tumors diagnosed within one year of the diagnosis of Barrett's esophagus, the incidence rate of adenocarcinoma was 1.5 (95% CI 0.9-2.0) per 1,000 person-years at risk, with a median time to diagnosis of 2.5 years (Table 3). The standardized incidence ratio of esophageal adenocarcinoma was 9.4 (95% CI 6.2-13.6). The incidence rate of the compound endpoint adenocarcinoma or high-grade dysplasia was 3.0 (95% CI 2.2-3.7) per 1,000 person-years at risk, with a median time to diagnosis of 2.0 years. High-grade dysplasia always occurred with a diagnosis of Barrett's esophagus, and standardized incidence ratio for this outcome was thus not possible to calculate.

Table 3. Risk of esophageal adenocarcinoma and high-grade dysplasia among 7,932 participants with Barrett's esophagus.

	Events	Person-years at risk	Incidence rate ^a (95%CI)	Standardized incidence ratio (95%CI)
Adenocarcinoma				
Total	27	18,415	1.47 (0.91-2.02)	9.36 (6.16-13.61)
Age (years)				
30-49	4	1,782	2.24 (0.04-4.44)	188.86 (50.81-483.52)
50-69	9	9,599	0.94 (0.33-1.55)	7.46 (3.40-14.17)
≥70	14	7,034	1.99 (0.95-3.03)	8.44 (4.61-14.16)
Sex				
Women	5	6,041	0.83 (0.10-1.55)	17.02 (5.49-39.72)
Men	22	12,374	1.78 (1.03-2.52)	8.49 (5.32-12.85)
High-grade dysplasia				
Total	27	18,424	1.47 (0.91-2.02)	N/A
Age (years)				
30-49	4	1,778	2.25 (0.04-4.45)	N/A
50-69	12	9,617	1.25 (0.54-1.95)	N/A
≥70	11	7,029	1.56 (0.64-2.49)	N/A
Sex				
Women	7	6,028	1.16 (0.30-2.02)	N/A
Men	20	12,396	1.61 (0.91-2.32)	N/A

^aPer 1,000 person-years

5.2 STUDY II

After retrieval of medical records from 71 Swedish hospitals, the final study cohort consisted of 279 cases of adenocarcinoma/high-grade dysplasia and 1,089 controls with Barrett's esophagus. The participation proportion was 90%. Mean age was 65 years and 71% were male (Table 4). The diagnosis of Barrett's esophagus was verified by endoscopy with biopsy in 81% of index endoscopies, of which 96% showed metaplastic columnar cells.

Table 4. Characteristics of 1,368 study participants with Barrett's esophagus.

	Number (%)		
	EAC (n=151)	HGD (n=128)	Controls (n=1,089)
Age (years) – mean (standard deviation)	67.5 (10.5)	68.1 (10.8)	64.3 (12.1)
Sex			
Women	17 (11.3)	20 (15.6)	358 (32.9)
Men	134 (88.7)	108 (84.4)	731 (67.1)
Segment length (cm) – median (interquartile range)			
Maximum	6 (4-10)	5 (2-10)	2 (1-5)
Circumferential	4 (0-8)	2 (0-7)	0 (0-2)
Hernia size (cm) – median (interquartile range)	4 (2-5)	3 (3-5)	3 (2-5)
Esophagitis	71 (47.0)	85 (66.4)	598 (54.9)

Abbreviations: EAC – esophageal adenocarcinoma, HGD – high-grade dysplasia

Table 5 shows adjusted ORs with 95% CIs for the primary and secondary outcomes. In the multivariable analysis, older age, male sex and increasing segment length at diagnosis were associated with increased risk of adenocarcinoma and/or high-grade dysplasia. A prediction model based on the variables age, sex and segment length predicted 71% of the compound endpoint adenocarcinoma or high-grade dysplasia (Figure 7), 75% of all adenocarcinoma and 68% of all high-grade dysplasia. Hiatal hernia and reflux esophagitis did not improve the model (Table 5).

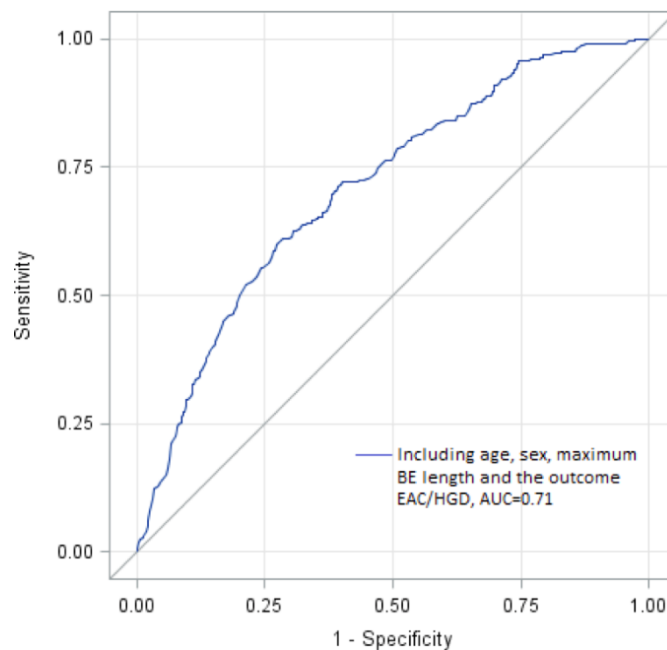


Figure 7. Prediction model of progression to adenocarcinoma or high-grade dysplasia (EAC/HGD) among patients with Barrett's esophagus (BE) described in a receiver operating characteristic curve. AUC –area under the curve

Table 5. Prediction of esophageal adenocarcinoma or high-grade dysplasia (EAC/HGD) after multiple imputation (including participants with missing data).

	Number (%)		Adjusted ^a odds ratio with 95%CI
	EAC/HGD (n=279)	Controls (n=1,089)	
Age (year)			
Continuous	-	-	1.02 (1.01-1.03)
Sex			
Women	37 (13.3)	358 (32.9)	1.0 (Reference)
Men	242 (86.7)	731 (67.1)	2.8 (1.9-4.1)
Segment length			
Ultra-short (<1 cm)	23 (8.2)	195 (17.9)	1.0 (Reference)
Short (1 to <3 cm)	45 (16.1)	338 (31.0)	1.1 (0.7-1.9)
Long (3 to <8 cm)	97 (34.8)	302 (27.7)	2.3 (1.4-3.9)
Ultra-long (≥8 cm)	89 (31.9)	143 (13.1)	4.3 (2.5-7.2)
Hiatal hernia			
No	60 (21.5)	219 (20.1)	1.0 (Reference)
Yes	219 (78.5)	870 (79.9)	0.8 (0.6-1.1)
Esophagitis			
No	123 (44.1)	491 (45.1)	1.0 (Reference)
Yes	156 (55.9)	598 (54.9)	1.1 (0.8-1.4)

^aAdjusted for age, sex, maximum segment length, hiatal hernia, esophagitis

5.3 STUDY III

Among 211 study participants with Barrett's esophagus followed for median 3.9 person-years (interquartile range 2.2-5.6 years), 149 (71%) had low-grade dysplasia and 62 (29%) had high-grade dysplasia. Mean age was 67 years and 81% were male (Table 6). Surveillance of Barrett's esophagus was the most common indication for endoscopy (62%) and 46% had undergone two or more previous endoscopies.

Table 6. Characteristics of 211 study participants with dysplastic Barrett's esophagus.

	Number (%)	
	LGD (n=149)	HGD (n=62)
Age (years) – mean (standard deviation)	66.3 (9.2)	68.7 (10.8)
Sex		
Women	32 (21)	8 (13)
Men	117 (79)	54 (87)
Charlson comorbidity index		
0	87 (58)	31 (50)
≥1	62 (42)	31 (50)
Segment length (cm) – median (interquartile range)		
Maximum	5 (2-9)	5 (3-9)
Circumferential	1 (0-6)	3.5 (0-9)
Hiatal hernia	110 (74)	52 (84)

Abbreviations: HGD – high-grade dysplasia, LGD – low-grade dysplasia

In total, 84% of the participants underwent a follow-up endoscopy, 17% underwent endoscopic therapy and 8% underwent esophagectomy during follow-up (Table 7). However, 60% of all participants were not followed-up or treated in adherence to guidelines, mainly due to underutilization of surveillance (86%). Median time to first follow-up endoscopy was 9 months, to endoscopic treatment 13 months and to esophagectomy 17 months.

Table 7. Clinical management of 211 participants with dysplastic Barrett's esophagus.

	Number (%)	
	LGD (n=149)	HGD (n=62)
Deviation from surveillance guidelines	103 (69)	24 (39)
Under-surveillance	85 (83)	24 (100)
Over-surveillance	18 (17)	0 (0)
Follow-up endoscopy	117 (79)	60 (97)
Endoscopic therapy	12 (8)	24 (39)
Esophagectomy	5 (3)	12 (19)
Death	12 (8)	15 (24)
Median time to follow-up endoscopy (in months)	13	3
Median time to endoscopic therapy (in months)	39	7
Median time to esophagectomy (in months)	26	6

Abbreviations: HGD – high-grade dysplasia, LGD – low-grade dysplasia

Table 8 shows risk factors for deviation from clinical guidelines. Low-grade dysplasia and long-segment Barrett's esophagus were associated with increased odds of deviation from guidelines compared to high-grade dysplasia and short-segment Barrett's esophagus, respectively. In addition, deviation from guidelines was more common in gastroenterological departments in comparison to surgical departments.

Table 8. Risk factors for deviation from guidelines in 211 participants with dysplastic Barrett's esophagus.

	Number (%)		Adjusted ^a odds ratio with 95%CI
	Deviation from guidelines (n=127)	Adherence to guidelines (n=84)	
Age (years)			
<65	47 (37)	34 (40)	1 (Reference)
≥65	80 (63)	50 (60)	1.1 (0.6-2.1)
Sex			
Men	100 (79)	71 (85)	1 (Reference)
Women	27 (21)	13 (15)	1.4 (0.6-3.1)
Comorbidity			
0	70 (55)	48 (57)	1 (Reference)
≥1	57 (45)	36 (43)	1.7 (0.8-3.5)
Dysplasia			
High-grade	24 (19)	38 (45)	1 (Reference)
Low-grade	103 (81)	46 (55)	3.4 (1.7-6.8)
Segment length			
Short (<3 cm)	34 (30)	30 (40)	1 (Reference)
Long (≥3 cm)	80 (70)	45 (60)	2.0 (1.0-3.9)
Department			
Surgery	51 (40)	53 (63)	1 (Reference)
Gastroenterology	70 (55)	29 (34)	2.3 (1.2-4.4)
Other	6 (5)	2 (3)	8.1 (0.7-91.5)

^aAdjusted for age, sex, comorbidity, the degree of dysplasia, segment length, calendar period, hospital and department.

5.4 STUDY IV

Among 6,600 study participants with newly diagnosed esophageal adenocarcinoma followed for 9,138 person-years (mean 1.4 years), median age was 70 years and 79% were male (Table 9). Of all participants, 7% had a history of GERD and 9% had undergone at least one endoscopy before adenocarcinoma diagnosis.

Table 9. Characteristics of 6,600 study participants with esophageal adenocarcinoma.

	Number (%)	
	GERD (n=440)	No GERD (n=6,160)
Age (years)		
≤55	38 (8.6)	765 (12.4)
56-65	112 (25.5)	1,448 (23.5)
66-75	136 (30.9)	1,879 (30.5)
≥76	154 (35.0)	2,068 (33.6)
Sex		
Women	83 (18.9)	1,281 (20.8)
Men	357 (81.1)	4,879 (79.2)
Charlson comorbidity index		
0	260 (59.1)	4,209 (68.3)
1	111 (25.2)	1,368 (22.2)
≥2	69 (15.7)	583 (9.5)
Tumor stage^a		
I	52 (22.5)	225 (6.4)
II	66 (21.0)	597 (17.1)
III-IV	126 (40.0)	1,932 (55.3)
Unstaged	71 (22.5)	739 (21.2)
Surgical resection of adenocarcinoma	166 (37.7)	2,030 (33.0)

^aTumor stage data were available for patients diagnosed with adenocarcinoma in 2005-2013 (n=3,808)

Abbreviations: GERD – gastroesophageal reflux disease

The cumulative proportion of death in adenocarcinoma was decreased for participants with GERD and in participants with ≥3 previous endoscopies (Figure 8 and 9). Moreover, the adjusted 5-year mortality in adenocarcinoma was decreased in participants with GERD compared to those without GERD (adjusted HR 0.71, 95% CI 0.64-0.80). This association was only slightly attenuated by further adjustment for previous endoscopies (adjusted HR 0.79, 95% CI 0.70-0.90), tumor stage and surgical resection (adjusted HR 0.74, 95% CI 0.62-0.89). Patients with GERD had increased odds of surgical resection (adjusted OR 1.39, 95% CI 1.13-1.71), which remained after adjustment by previous endoscopies (adjusted OR 1.30, 95% CI 1.01-1.67).

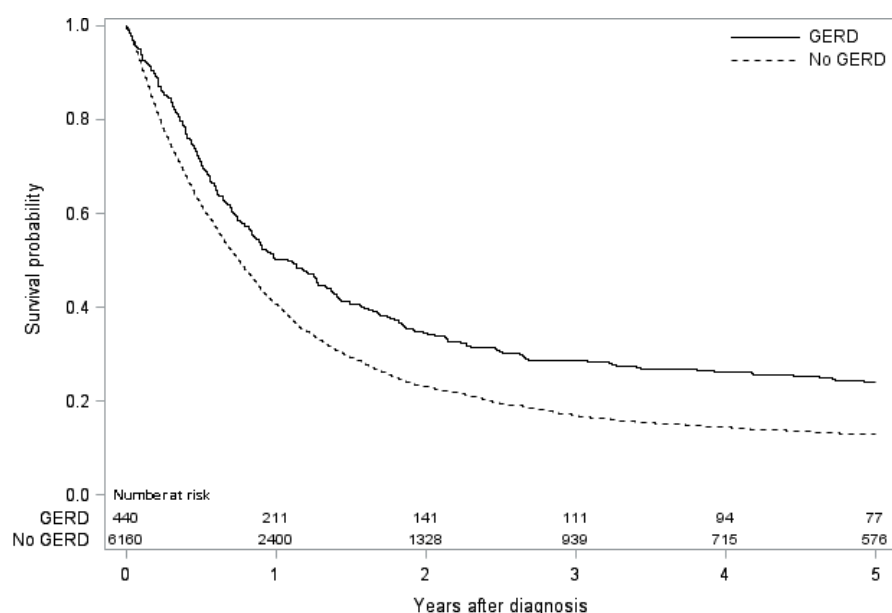


Figure 8. Cumulative disease-specific mortality after diagnosis of esophageal adenocarcinoma among patients with and without gastroesophageal reflux disease (GERD).

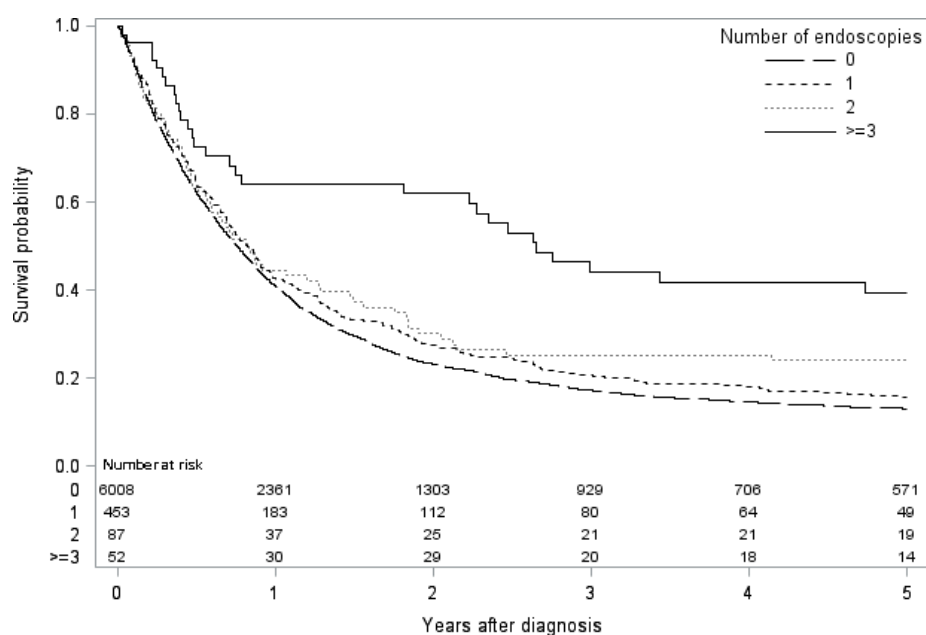


Figure 9. Cumulative disease-specific mortality after diagnosis of esophageal adenocarcinoma stratified by number of endoscopies prior to esophageal adenocarcinoma.

The adjusted HR for mortality in adenocarcinoma among participants with GERD was virtually unaltered for 1 or 2 previous endoscopies compared to 0 endoscopies, while ≥ 3 previous endoscopies was associated with decreased 5-year mortality (Table 10). The odds ratio of surgical resection increased with number of previous endoscopies in patients in

GERD, but was not statistically significant (Table 10). In participants without GERD, endoscopies were not associated with 5-year mortality or surgical resection (Table 11).

Table 10. Risk of disease-specific 5-year mortality and surgical resection rates among 440 participants with esophageal adenocarcinoma and gastroesophageal reflux disease

	Number (%)			
	No endoscopy 170 (38.6)	1 endoscopy 168 (38.2)	2 endoscopies 56 (12.7)	≥3 endoscopies 46 (10.5)
5-year mortality^a (HR, 95%CI)	1 (Reference)	1.0 (0.8-1.3)	0.9 (0.6-1.3)	0.6 (0.4-0.9)
Surgical resection^a (OR, 95%CI)	1 (Reference)	0.7 (0.4-1.1)	1.2 (0.6-2.3)	1.9 (0.9-3.7)

^aAdjusted for age, sex, calendar year and comorbidity

Abbreviations: HR – hazard ratio, OR – odds ratio

Table 11. Risk of disease-specific 5-year mortality and surgical resection rates among 6,160 participants with esophageal adenocarcinoma and no gastroesophageal reflux disease

	Number (%)			
	No endoscopy 5,838 (94.8)	1 endoscopy 285 (4.6)	2 endoscopies 31 (0.5)	≥3 endoscopies 6 (0.1)
5-year mortality^a (HR, 95%CI)	1 (Reference)	0.9 (0.8-1.0)	0.9 (0.6-1.4)	1.0 (0.4-2.3)
Surgical resection^a (OR, 95%CI)	1 (Reference)	0.9 (0.7-1.2)	1.7 (0.8-3.6)	0.6 (0.1-5.5)

^aAdjusted for age, sex, calendar year and comorbidity

Abbreviations: HR – hazard ratio, OR – odds ratio

6 METHODOLOGICAL CONSIDERATIONS

6.1 STUDY DESIGN

Clinical research is conducted either by experimental or observational design. Experimental studies are most often conducted as randomized controlled trials, while cohort and case-control designs are common in observational studies and were used for this thesis. If the sample size is large enough, randomized studies typically leads to two (or more) groups of participants which are alike in all aspects but one – the exposure status – which allows for a direct causal interpretation of the relation between exposure and outcome. In contrast, the exposed and non-exposed participants in observational studies are often different, which introduces a risk of confounding (discussed below). While the investigator in observational studies attempts to control for confounding, the obtained measure of association may not always be causally interpreted because of the influence of residual confounding factors.

Nevertheless, observational studies hold many advantages compared to randomized studies and may be conducted in settings where randomized studies are not feasible. Some exposures are not possible to randomize, e.g. due to ethical or biological reasons, and rare outcomes may be unsuited to study because of the vast study sample size required to randomize to obtain precise results. Randomized studies are often limited to strict inclusion criteria, why the results may not always be inferred to an intended source population or generalizable to other populations. In contrast, observational studies may allow for the study of unselected and large study populations, which increases the external validity and precision and also allows for a number of exposures and outcomes to be examined in the same cohort.

6.2 INTERNAL VALIDITY

Internal validity refers to how well the observed estimate or association from the sampled study population represents the true estimate or association in the source population. The internal validity of a study may be compromised by a set of errors typically categorized into two main subheadings: systematic error, further subcategorized into selection bias, information bias and confounding, and random error.

6.2.1 Selection bias

Selection bias is a systematic error which occurs when the participants in a study are a selected subpopulation which does not represent the population that the results are inferred upon. The consequence might be that the association between exposure and outcome among the included participants is different from the association in those eligible for the study.¹⁰³ Typically, the risk of selection increases when participation is voluntary or patients are lost to follow-up. In this thesis, follow-up was complete in all studies due to the use of nationwide registers. Study I and IV were nationwide studies and included virtually all patients in Sweden diagnosed with Barrett's esophagus and adenocarcinoma, which minimized selection. Study II and III consisted of all patients with adenocarcinoma or high-grade dysplasia within the Barrett's esophagus cohort, and a random sample of patients without dysplasia or low-grade dysplasia. Medical records were unavailable for a tenth of the included participants, which introduces a small risk of selection. Data were also missing for some the variables obtained from medical records, including segment length, hiatal hernia size and severity of esophagitis. Multiple imputation analysis was used to account for the limited missing data on segment length, but the proportion of missing was substantial for hiatal hernia size and severity of esophagitis. To minimize selection and preserve internal validity, hiatal hernia size and grade of esophagitis were not studied as predictors of tumor progression.

6.2.2 Information bias

Information bias refers to the misclassification of study variables. Information bias can be non-differential, meaning that the misclassification is equal among the comparison groups in a study. Non-differential misclassification results in an underestimation, or dilution, of the effect size. Differential misclassification, where the assessment of exposure or outcome varies over groups, is more unpredictable and may bias the measure of association in any direction. In contrast to selection bias, the amount of misclassification can be estimated in comparison to a gold standard, often described by the sensitivity or specificity.¹⁰⁴ Sensitivity describes the probability of detecting an outcome in an individual with the outcome, while specificity describes the probability of testing negative in an individual without the outcome. The registers used in this thesis have been extensively validated with good results, including specific validation of the diagnosis of adenocarcinoma, which should reduce the risk of

misclassification. Further, the diagnosis of Barrett's esophagus was validated by manual review of medical records in Study II and III.

6.2.3 Confounding

Confounding occurs when the exposure is associated with a variable which also impacts on the outcome, but is not along the causal pathway from exposure to outcome. Confounding is a problem in most observational studies because of the risk of residual confounding by unknown variables which cannot be adjusted for. However, known confounders can be managed in a few different ways. Confounding may be handled prior to sampling by matching on the confounding variable. After data collection, confounding can be managed by stratification on the confounding variable or by adjusting for confounding variables in multivariable regression models. For the first three studies in this thesis confounding was a minor problem. Study I and III were descriptive studies and Study II was a prediction model. In a prediction model, confounding by other variables is less relevant as long as the model performs well. However, other predictors for esophageal adenocarcinoma, such as smoking and obesity, could have improved the model but are only registered in medical registers in the odd case. In Study IV, GERD was associated with improved survival in adenocarcinoma after adjustment for most established prognostic factors. However, the mechanism for the improved survival is largely unknown and may well be the result of residual confounding by unknown factors associated with both GERD and survival in adenocarcinoma rather than GERD itself.

6.2.4 Random error

After eliminating any systematic error, random error may influence the internal validity of a study. The amount of random error in a study is described by the precision, which in turn is described by the confidence interval. The 95% confidence interval indicates that if a study was repeated and free from systematic error, it would contain the true measure within the interval 95% of the time. If the interval is narrow, there is high precision and thus low amount of random error, and vice versa. Large sample sizes, typically available in nationwide studies, narrow the confidence interval and reduce the amount of random error.

The p-value, which is complementary to the 95% confidence interval, describes the probability of rejecting a true null hypothesis in the absence of systematic non-random error (type I error). A p-value below 0.05 is traditionally considered satisfactory and leads to a rejection of the null hypothesis in favor of the alternative hypothesis. Importantly, hypothesis testing never provides a definitive rejection of the null hypothesis, but rather only a probability that the null hypothesis is true or false.¹⁰⁴

Although Study III was based on all high-grade dysplasia and a significant proportion of low-grade dysplasia in Sweden, the rarity of known dysplastic Barrett's esophagus resulted in a small sample size, which limited the precision of the study. Thus, the confidence intervals were wide, with an entailing increased risk of rejecting a true alternative hypothesis (type II error).

6.3 EXTERNAL VALIDITY

In contrast to internal validity, which concerns inference from the study population to the source population, external validity concerns inference from the study population to other populations or settings (generalizability). All studies in this thesis were population-based in design and had high participation rates, which means that results are highly generalizable to the Swedish population and to settings similar to Sweden.

7 GENERAL DISCUSSION

7.1 STUDY I

The main finding of Study I was that the absolute risk of tumor progression in Barrett's esophagus is low compared to historical estimates, which adds to similar research published in recent years.^{27, 28} Historically, the risk of adenocarcinoma in Barrett's esophagus had been estimated to be up to 3% per person-year at risk.¹⁰⁵ The cause of the much lower incidence of adenocarcinoma reported in recent years is likely attributable to several causes. First, a systematic review and meta-analysis suggested that the risk of adenocarcinoma reported in historical studies was overestimated due to suspected publication bias.¹⁰⁵ Second, the expansion of the definition of Barrett's esophagus to also include short segments should decrease the risk estimates, because short-segment Barrett's esophagus is associated with a lower risk of adenocarcinoma compared to long-segment Barrett's esophagus.¹⁰⁶⁻¹⁰⁹ Third, the increasing use of high-dose proton pump inhibitors may decrease tumor progression in Barrett's esophagus.^{60, 61} In contrast, the use of preventive endoscopic therapy likely had a limited impact, given that radiofrequency ablation for low-grade dysplasia was not recommended until more recently.

A surprising finding of the study was the unexpectedly high proportion of patients diagnosed with adenocarcinoma within one year of Barrett's diagnosis, which was comparable to the proportion in a similarly designed Danish population-based study.²⁸ The high proportion of early diagnosed adenocarcinoma is likely a result of prevalent adenocarcinomas missed upon initial diagnosis of Barrett's esophagus. A recent meta-analysis estimated the proportion of missed adenocarcinomas diagnosed within one year of Barrett's esophagus to 25%, but with considerably heterogeneous results in-between studies.¹¹⁰ There is no apparent systematic explanation for the heterogeneity, which is stable over calendar-year, study setting and geographical origin.¹¹⁰ Nevertheless, this finding highlights the importance of awareness of early neoplasia in Barrett's esophagus. Early neoplasia is notoriously difficult to detect, but training by fairly simple means may improve detection rates considerably.¹¹¹ The availability of advanced diagnostic tools to promptly detect neoplasia in Barrett's esophagus, such as narrow-band imaging and wide area trans-epithelial sampling may also improve the detection rate.^{112, 113}

Only a minute proportion of all esophageal adenocarcinomas in Sweden during the study period arose in patients diagnosed with Barrett's esophagus. The proportion of

adenocarcinomas with a known previous diagnosis of Barrett's esophagus was lower compared to previous reports,¹¹⁴ which is worrying because adenocarcinoma presenting without a prior diagnosis of Barrett's esophagus is associated with a dismal prognosis.

Among the study's methodological strengths were the nationwide design, the large sample size and the complete follow-up. Paired with the use of validated registers, the study secured results which should be generalizable to similar Western populations. Among the limitations were the inability to stratify the cohort for low-grade dysplasia and the relatively short median follow-up time. Yet, the impact of including Barrett's esophagus with low-grade dysplasia should be limited because 90-95% of Barrett's esophagus is negative for dysplasia and the risk of adenocarcinoma in low-grade dysplasia is only moderately increased.²⁹

7.2 STUDY II

Study II showed that it may be possible to tailor surveillance of Barrett's esophagus by using readily available demographic and endoscopic variables. Tailoring of surveillance programs in Barrett's esophagus is highly needed, given that the vast majority of patients will not progress to adenocarcinoma, rendering general surveillance inefficient and costly.^{54, 55} The main finding was that 71% of esophageal adenocarcinoma and high-grade dysplasia could be explained by three variables: age, sex and maximum segment length, which was comparable to and adds support to simultaneously published clinical prediction models.^{115, 116} While the precision was fair, the model needs improvement for use in clinical practice. A recent meta-analysis of risk factors for tumor progression in Barrett's esophagus indicated that apart from older age, male sex, and longer segment length, cigarette smoking and low-grade dysplasia increase the risk of tumor progression to esophageal adenocarcinoma, while use of proton-pump inhibitors or statins decrease the risk.¹⁰⁹ However, incorporation of these additional risk factors in more complex models had a limited effect on the model performance. The addition of smoking and low-grade dysplasia to age, sex and segment length only resulted in a modestly improved prediction model in a multicenter study from the US and the Netherlands.¹¹⁵ In another study from the US, which added use of proton pump inhibitors and history of esophageal candidiasis to the model, the performance of the prediction model was also similar.¹¹⁶ Taken together, the results from this thesis and recently published clinical models imply that additional factors, such as biomarkers, are needed to improve the performance of future prediction models.^{117, 118}

Apart from outlining the prediction model, the study demonstrated with good precision that once Barrett's esophagus is diagnosed, neither hiatal hernia nor esophagitis are risk factors for progression to esophageal adenocarcinoma. Thus, while hiatal hernia and esophagitis are part of the causal pathway from GERD to esophageal adenocarcinoma, the presence or history of these lesions are less important once Barrett's esophagus has developed, which is a clinically valuable finding.

A third contribution of this study was the validation of the ICD code for Barrett's esophagus in the Patient Register. Overall, the proportion of patients biopsied and the presence of metaplastic epithelium in vast the majority of biopsy specimens indicated overall good quality of the diagnosis code in the Patient Register. Nevertheless, only one endoscopy per study participant was reviewed, and any subsequent or precedent endoscopy could further improve the validity of the ICD code in the Patient Register.

This was one of the largest studies to date assessing endoscopic risk factors for tumor progression in Barrett's esophagus. Among the methodological strengths were the extensive data collection and the large sample size, which allowed for precise risk estimates. The nationwide design, high participation rate and low proportion of missing data resulted in a study cohort with low risk of selection bias. Possibly, additional clinical variables which were not available could have improved the performance of the model. Information on proton pump inhibitor medication was available, but was not evaluated because of the ubiquitous use among the study participants. Moreover, a substantial proportion of patients did not have specialized intestinal metaplasia upon index endoscopy. This could limit the generalizability to the broader definition of Barrett's esophagus recommended by the British Society of Gastroenterology, which defines Barrett's esophagus as all metaplastic columnar epithelium above the gastroesophageal junction.²⁴

7.3 STUDY III

The main finding of Study III was that while gastroenterological societies recommend surveillance or outright treatment of Barrett's esophagus with dysplasia, these guidelines are often not enforced in clinical practice. Several risk factors for deviation from guidelines were identified. Compared to Barrett's esophagus with low-grade dysplasia, adherence was better in high-grade dysplasia, indicating that the physicians are stricter in the management of high-risk lesions. Long-segment Barrett's esophagus was associated with underutilization of surveillance and treatment, but has conversely been associated with overutilization of

surveillance endoscopy in non-dysplastic Barrett's esophagus.¹¹⁹ Somewhat surprisingly, clinical guidelines were less strictly enforced in gastroenterological departments compared to surgical departments. While surgeons may be more commonly involved in high-grade dysplasia or early adenocarcinoma, this association was robust and remained after adjustment for baseline dysplasia. Speculatively, because gastroenterologists often are medically responsible for the surveillance of Barrett's esophagus, they might more often consciously deviate from guidelines. Questionnaire data have indicated that gastroenterologists mostly adhere to guidelines, but tailor the surveillance further based on the endoscopic appearance.^{120, 121}

This study expands on previous studies of adherence to surveillance guidelines in non-dysplastic Barrett's esophagus, which is reported to be poor.^{119, 122-124} Surveillance of Barrett's esophagus is associated with improved outcomes in adenocarcinoma, why efforts to improve adherence to guidelines in clinical practice are beneficial and needed.⁵²

Methodological strengths of the study included the population-based design, the extensive data collection, validation of the diagnosis of Barrett's esophagus through manual review of histopathology reports and the complete follow-up. Limitations include that in some cases deviation from guidelines may have been voluntary due to patient frailty and refusal by the patient to participate. While this would result in a deviation from guidelines, it should not be considered inappropriate management. Despite the nationwide design, the sample size was relatively small, which resulted in wide confidence intervals and risk of type II errors. Whether these variables are associated with poor surveillance and treatment should be assessed in larger studies or meta-analyses.

7.4 STUDY IV

The main findings of Study IV were that GERD was associated with improved prognosis in esophageal adenocarcinoma, but that the increased use of endoscopy screening in these patients did not explain the improved survival. Survival was virtually unaltered in patients with 1-2 endoscopies before adenocarcinoma diagnosis, while survival improved substantially in patients with GERD and ≥ 3 endoscopies before adenocarcinoma diagnosis.

Previous literature has provided sparse and contradictory data on whether endoscopy screening for GERD improves survival in esophageal adenocarcinoma. The aggressive nature of esophageal adenocarcinoma leaves a short time window for detection, requiring perfect

timing of the endoscopy to detect curable cancer. In addition, the tumor often develops without symptoms, why the detection of early stage adenocarcinoma represents a major challenge to most physicians. Nevertheless, a high rate of referral for endoscopy in a general practice setting has been associated with improved outcomes in esophageal and gastric cancer.¹²⁵ In smaller studies, a screening endoscopy for GERD within a few years of esophageal adenocarcinoma diagnosis has been associated with earlier tumor stage and increased surgical resection rates.^{126, 127} In this study, the use of endoscopy was not associated with improved survival unless performed frequently, which indicates a limited role for endoscopy screening in the prevention of mortality in esophageal adenocarcinoma. A group of patients at high risk of adenocarcinoma may benefit from repeat endoscopy for GERD, although it remains a challenge to select these patients and the ideal interval for endoscopies. Repeated endoscopy for other indications than GERD should have a similar effect on detecting adenocarcinoma, although the study was not powered to verify or reject this hypothesis. Nevertheless, a history of GERD was associated with improved survival in adenocarcinoma, although the improved prognosis was not explained by increased use of endoscopy screening or earlier tumor stage in these patients. While established prognostic factors were adjusted for, the improved survival in GERD-associated adenocarcinoma may be due to residual confounding by other factors such as health-conscious behavior or therapy associated with GERD.

Methodological strengths of the study included the nationwide design, which secured an unselected, large cohort with complete follow-up, and the possibility to assess the impact of multiple endoscopies for GERD. Among the limitations was the inability to account for some potential confounding factors which might explain the improved prognosis in GERD-related adenocarcinoma. Further, the occurrence of GERD was likely underestimated, because GERD is not always reported by patients. It is likely that less severe GERD remained undiagnosed and more severe GERD was registered. Because those with less severe GERD were considered unexposed, this should dilute the association between GERD and mortality in adenocarcinoma.

8 CONCLUSIONS

- The absolute risk of esophageal adenocarcinoma in Barrett's esophagus is limited, particularly after the first year of diagnosis, indicating that general surveillance of these patients may be ineffective.
- By using clinical patient characteristics such as age, sex and length of the Barrett segment, it is possible to identify patients at increased risk of adenocarcinoma and tailor surveillance programs.
- Surveillance and treatment guidelines for the management of Barrett's esophagus are poorly followed in clinical practice, which indicates that efforts to implement guidelines should be made.
- GERD is associated with improved outcomes in esophageal adenocarcinoma, but the use of endoscopy screening in these patients does not improve survival in adenocarcinoma unless performed repeatedly. These findings indicate that other strategies to detect curable adenocarcinoma are needed.

9 FUTURE DIRECTIONS

Prediction modelling based on clinical factors have indicated that further risk stratification of Barrett's esophagus is possible with some accuracy.^{115, 116, 128} However, these models need to be improved to more confidently exclude patients with low risk of adenocarcinoma from surveillance programs. Research in recent years has identified an abundance of biomarkers in esophageal tissue and blood associated with tumor progression in Barrett's esophagus.^{117, 118, 129, 130} A combination of clinical variables and biomarkers could improve current models and should be further evaluated in future studies.

Two further strategies may be used to decrease mortality in esophageal adenocarcinoma. First, efforts to implement guideline recommendations for surveillance and treatment of Barrett's esophagus in clinical practice should be made, because appropriate surveillance of Barrett's esophagus likely leads to improved survival in adenocarcinoma.⁵² Second, the detection of Barrett's esophagus needs to be improved. While endoscopic screening based on GERD may be invasive, costly and ineffective, preliminary data from non-endoscopic screening methods for the detection of Barrett's esophagus have shown promising results.¹³¹⁻¹³⁵ The use of such minimally invasive methods may move the diagnostic tools for identifying Barrett's esophagus from endoscopists in specialized healthcare to a primary care setting, thus increasing the availability significantly.

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

10.1 BAKGRUND

Sjuklig grad av halsbränna, även kallat gastroesofageal refluxsjukdom, är mycket vanligt och kan oftast behandlas framgångsrikt med receptfria mediciner. Refluxsjukdom är för det mesta ett godartat tillstånd, men i ett fåtal fall kan långvariga besvär ge upphov till en cancertyp i matstrupen (körtelcancer). Förekomsten av denna typ av matstrupscancer har de senaste decennierna ökat snabbt, vilket troligen delvis beror på den ökade förekomsten av övervikt, vilket kan orsaka besvär med reflux. Matstrupscancer är en symptomfattig tumörsjukdom med mycket aggressivt förlopp, vilket innebär att många diagnosticeras sent i förloppet. Således är prognosen dålig och endast ca 20 % lever fem år efter diagnos. Tumören föregås av utbredda förändringar i matstrupens slemhinna som kallas Barretts esofagus, synligt för ögat som en rödare slemhinna vid gastroskopi. Detta tillstånd finns hos 1-2% av alla vuxna. Patienter med Barretts esofagus följs med upprepade gastroskopier för att diagnosticera, förebygga och behandla matstrupscancer i botbart skede. Den stora majoriteten av patienter med Barretts utvecklar dock aldrig matstrupscancer och följs därför i onödan.

Det övergripande målet med den här avhandlingen var att utvärdera risk och prognos för matstrupscancer hos patienter med Barretts esofagus. För detta ändamål användes data från nationella register och insamlade journaluppgifter från 1,368 patienter med Barretts esofagus.

10.2 METODER OCH RESULTAT

Studie I utvärderade risken för matstrupscancer hos patienter med Barretts esofagus.

Samtliga patienter med diagnosticerad Barretts esofagus i svenska patientregistret identifierades och följdes avseende på risk för matstrupscancer diagnosticerat i svenska cancerregistret. I de fall cancer inte diagnosticerats följdes patienterna till emigrations- eller dödsdatum, vilket identifierades via svenska befolkningsregistret, eller till studieperiodens slut. Totalt identifierades 7,932 patienter med Barretts esofagus, varav 89 patienter utvecklade matstrupscancer. De flesta tumörer diagnosticerades inom ett år efter diagnosen Barretts esofagus ställts och många av dessa förekom sannolikt redan vid den initiala diagnosen av Barretts esofagus. Efter det första året var risken för matstrupscancer mycket låg. Den årliga risken för cancer uppskattades till 0.15 %, vilket dock fortfarande var 9.4 gånger högre än i den totala befolkningen i samma ålder, kön och kalenderår som de med

Barretts esofagus. Huvudbudskapet i denna studie var att patienter med Barretts esofagus har en lägre risk för matstrupscancer än man tidigare trott.

Studie II utvärderade om patienter med Barretts esofagus kan klassas som hög- eller lågriskpatienter baserat på klinisk information såsom ålder, kön samt det endoskopiska utseendet av den förändrade slemhinnan. Patienter som utvecklat matstrupscancer eller dess förstadium (höggradig dysplasi) identifierades i patient- och cancerregistret och inkluderades som fall. Den kliniska informationen och endoskopibilden hos dessa patienter jämfördes med samma information hos kontrollpatienter med Barretts esofagus utan matstrupscancer eller höggradig dysplasi. Totalt identifierades 1,525 patienter vars journaluppgifter samlades in från sjukhus i hela Sverige. I slutändan inkluderades 1,368 patienter, varav 279 hade utvecklat matstrupscancer eller höggradig dysplasi. Efter genomgång av journaluppgifterna visade sig några variabler vara riskfaktorer för tumörutveckling: hög ålder, manligt kön och längre utbredning av Barretts esofagus. Andra misstänkta riskfaktorer, såsom inflammation i matstrupen och hiatusbråck, vilka båda är starkt kopplade till gastroesofageal refluxsjukdom, visade sig dock inte öka risken för matstrupscancer. En statistisk modell som byggde på de tre riskfaktorerna kunde förutsäga 71 % av matstrupscancrar, vilket kan anses vara acceptabel precision för att kunna bidra till en framtida mer skräddarsydd handläggning av patienter med Barretts esofagus.

Studie III utvärderade om behandling av Barretts esofagus med tidiga (låggradiga) eller avancerade (höggradiga) cellförändringar (dysplasi) i Sverige följer de medicinska riktlinjerna. Riktlinjerna rekommenderar uppföljande gastroskopi eller gastrokopisk behandling för att upptäcka eller förhindra matstrupscancer hos dessa patienter. Patienterna identifierades från Studie II och följdes upp med patient-, cancer- och dödsorsaksregistret. Totalt inkluderades 211 patienter från 50 sjukhus som följdes under i median 3.9 år. Under denna period genomgick 84 % en uppföljande endoskopi, 17 % genomgick gastrokopisk behandling och 8 % genomgick kirurgisk behandling av matstrupen. Dock var hela 60 % av handläggandet inte i enlighet med medicinska riktlinjer, huvudsakligen på grund av underanvändning och tidsfördröjning av gastroskopi och behandling. Riskfaktorer för avvikande handläggning var låggradiga (jämfört med höggradiga) cellförändringar och längre utbredning av Barretts esofagus. Riktlinjer följdes mer strikt vid kirurgiska kliniker än vid medicinska kliniker.

Studie IV utvärderade om användandet av magkikarundersökning (gastroskopi) för halsbränna minskar risken för död i matstrupscancer. Samtliga patienter i Sverige med matstrupscancer identifierades i cancerregistret och följdes med dödsorsaksregistret till och

med död eller till slutet av studieperioden. Tidigare diagnos av gastroesofageal reflux eller gastroskopi identifierades från patientregistret under en tidsperiod före insjuknandet i cancer. Totalt identifierades 6,600 patienter med matstrupscancer varav hade 7 % en diagnos av gastroesofageal refluxsjukdom och 9 % genomgått en tidigare gastroskopi. Risken för död i matstrupscancer var oförändrad hos patienter som genomgått en eller två tidigare endoskopier (jämfört med de som inte hade genomgått någon endoskopi), medan patienter med gastroesofageal refluxsjukdom och tre eller fler endoskopier hade 45 % lägre risk att dö i matstrupscancer jämfört med de som inte hade genomgått någon tidigare endoskopi.

10.3 DISKUSSION

Risken för matstrupscancer hos patienter med Barretts esofagus är relativt hög första året efter diagnos, medan risken därefter är mycket låg. Vårdgivare bör därför vara särskilt uppmärksamma på tecken till tumörsjukdom omedelbart efter att Barretts esofagus diagnosticerats. Kunskapen om att risken är särskilt hög hos äldre män med längre utbredning av Barretts esofagus kan användas för en mer skräddarsydd uppföljning i framtiden, men forskning bör först förbättra möjligheterna att finna patienter med särskilt hög risk för matstrupscancer. Majoriteten av patienterna med Barretts esofagus handläggs inte enligt medicinska riktlinjer, vilka behöver implementeras i klinisk praxis. Effekten av gastroskopier för att förebygga död i matstrupscancer är begränsad, varför alternativa metoder bör eftersökas.

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